REMARKS

Status of the Claims

Claims 1-4 and 6-19 are pending. Claims 2, 3, and 7-12 have been withdrawn from further consideration by the Examiner as being directed to a non-elected invention. Claims 1, 4, 6, and 13-19 are currently under consideration.

The Rejections Under 35 U.S.C. § 103(a)

Claims 1, 4, 6 and 13-19 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Schiffmann et al., *Proc. Natl. Acad. Sci. USA*, 97(1):365-370 (2000) (Schiffmann), or Desnick et al., *Proc. Natl. Acad. Sci. USA*, 76(10):5326-5330 (1979) (Desnick), each in view of Ziegler et al., *Human Gene Therapy* 10(10):1667-1682 (1999) (Ziegler) and Selden et al., WO 98/11206 (1998) (Selden).

The Office alleges that Schiffmann teaches infusing ten Fabry patients with α-galactosidase A (α-gal A), resulting in significantly reduced circulating globotriaosylceramide (Gb_3) levels in nine of the patients. The Office also alleges that Desnick teaches administration of α-gal A isozyme to 2 Fabry patients producing a 50-70% decrease in circulating Gb_3 concentration. The Office further alleges that Ziegler teaches preparation of an adenoviral vector encoding α-gal A and administration of the vector in a murine model of Fabry disease to obtain increased α-gal A expression accompanied by a reduction in circulating Gb_3 levels. Finally, the Office alleges that Selden teaches the treatment of Fabry disease patients either with transgenic human cells overexpressing and secreting α-gal A, or with purified recombinant human α-gal

A. The Office then concludes that it would have been obvious to one of ordinary skill in the art at the time of the invention to combine enzyme-replacement therapy as taught by Shiffman or Desnick with a vector encoding α-gal A as taught by Ziegler or with transgenic human cells expressing α-gal A as taught by Selden. Applicants respectfully submit that this conclusion is flawed for the following reasons.

The Claimed Invention Is Not *Prima Facie* Obvious

The Patent Office bears the burden to establish a *prima facie* case of obviousness under 35 U.S.C. § 103. *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988); *In re Deuel*, 51 F.3d 1552, 1557 (Fed. Cir. 1995). To support a rejection under § 103, the examiner must provide evidence showing "as a whole" that the legal determination sought to be proved is more probable than not. MPEP § 2142 (8th ed., 2nd revision, May, 2004). To satisfy this burden, the Office must first demonstrate some suggestion or motivation, whether in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the prior art references, or to combine the relevant teachings from the references. *Fine*, 837 F.2d at 1074; MPEP § 2143. Next, the Office must show that one of ordinary skill in the art would have had a reasonable expectation of success on modifying the prior art references, or on combining the relevant teachings from the references. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). Both the suggestion or motivation and the reasonable expectation of success *"must be founded in the prior art, not in the applicant's disclosure." Id.*

(emphasis added). Finally, the Office must show that the combined prior art references "teach or suggest all the claim[ed] limitations." MPEP § 2143.

The Examiner bears the initial burden of providing "some suggestion of the desirability of doing what the inventor has done." MPEP § 2142. To prove that a claimed invention is, more probably than not, obvious, the cited references "must expressly or impliedly suggest the claimed invention" with all its limitations, or the examiner "must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 U.S.P.Q. 972, 973 (Bd. Pat. App. & Inter. 1985); MPEP § 2142. Applicants respectfully submit that the Examiner has failed to meet this initial burden.

No Motivation Existed To Combine The References

When the motivation to combine the teachings of the references is not immediately apparent, "it is the duty of the examiner to explain why the combination of the teachings is proper." *Ex parte Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986); MPEP § 2142. To satisfy this duty, "the examiner must indicate the reasons *why* one skilled in the art" would have been motivated to combine the references. *Id.* (emphasis in original). Here the Examiner offers only the bare assertion that the combination of enzyme replacement therapy (taught by Desnick and Shiffmann) with gene therapy using a vector encoding α-gal A (taught by Zeigler) or using transformed human cells expressing α-gal A from a vector (taught by Selden) would have been obvious to one of ordinary skill in the art at the time of the invention "because either

administration of α-gal A protein or administration of a vector encoding α-gal A can reduce [Gb_3] level[s] in a subject with Fabry disease and Selden discusses that both gene therapy and enzyme replacement therapy can be used to treat Fabry disease patient[s.]" Office Action of Jan. 31, 2005, p. 4. This conclusory statement neither clearly explains the Examiner's argument that a skilled artisan would have been motivated to combine the references, nor demonstrates that the references expressly or impliedly suggest the claimed invention with all its limitations. Therefore Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness.

Applicants respectfully submit that there was no motivation to combine the teachings of Desnick or Shiffmann with the teachings of Ziegler or Selden. Both Desnick and Shiffmann teach treatment of Fabry disease by enzyme replacement therapy alone. Neither teaches the treatment of Fabry disease by gene therapy or with a small molecule of any kind, nor points out any side effects or other notable shortcomings of its teachings. Ziegler teaches treatment of Fabry disease by gene therapy using an adenoviral vector encoding α-gal A, co-administered with an immunosuppressant. Because the adenoviral vector frequently triggers an immune response after treatment, the combination taught by Ziegler is administered to treat the treatment, not to treat Fabry disease itself. Therefore there is no motivation to combine the teaching of Ziegler with the teachings of Desnick or Shiffmann, especially considering that neither Desnick nor Shiffmann observed any immunological side effects associated with enzyme replacement therapy. Further, although Ziegler observed that identification of the

mechanism for secretion and recapture of lysosomal enzymes via the mannose-6-phosphate receptor "provided a therapeutic rationale" for treatment of lysosomal storage disorders, s/he noted that that rationale was "based on **either** enzyme replacement **or** somatic gene therapy[,]" not on a combination of both. Ziegler, at 1668 (emphasis added).

Finally, Selden teaches the treatment of Fabry disease "**either** with (1) human cells that have been genetically modified to overexpress and secrete human α-gal A, **or** (2) purified human α-gal A obtained from cultured, genetically modified human cells." Selden, WO 98/11206, Abstract (emphasis added). Selden noted that, though pilot studies with enzyme replacement therapy have been conducted, "there is currently no effective treatment for Fabry disease[,]" indicating that neither enzyme replacement nor gene therapy effectively treats Fabry disease. Like Ziegler, Selden teaches treatment of Fabry disease by gene therapy, although Selden's method treats patients with transgenic cells modified to express α-gal A, not with a gene therapy vector encoding α-gal A alone. Similarly, Selden teaches that, in cases where cells cannot be obtained from the patient to be treated, administration of an immunosuppressant might be required. Therefore there is no motivation to combine the teaching of Selden with the teachings of Desnick or Shiffmann, especially considering that neither Desnick nor Shiffmann observed any immunological side effects associated with enzyme replacement therapy.

In addition, Selden repeatedly uses the disjunctive "or" to distinguish two potential methods of treatment: (1) gene therapy, **or** (2) enzyme replacement

therapy by conventional pharmaceutical administration of purified α-gal A. (Emphasis added); *see, e.g.*, Abstract; p. 2, lines 26-32; p. 14, lines 12-18; p. 14, line 32-p.15, line 2; p. 15, lines 10-16; p. 24, lines 8-11; and p. 33, lines 3-9. Despite Selden's consistent use of such language, and despite Selden's teaching that (1) sometimes gene therapy must be accompanied by administration of an immunosuppressant, and (2) neither enzyme replacement therapy nor gene therapy constitutes an effective treatment for Fabry disease, the Examiner nevertheless concludes that there was a motivation to combine Selden's teachings with those of Desnick or Shiffmann, based in large part upon Selden's statement that "individuals with α-gal A deficiencies **may also be** treated with purified α-gal A (i.e., enzyme replacement therapy)." (Examiner's emphasis). Applicants respectfully submit that both Ziegler and Selden teach two alternative, marginally effective methods of treating Fabry disease, and that neither Ziegler nor Selden provides a motivation to combine their teachings with those of Desnick or Shiffmann.

The Combined References Do Not Teach or Suggest the Claimed Invention With All Its Limitations

Both Desnick and Schiffman teach only the treatment of Fabry's disease by enzyme replacement therapy. Desnick examined *in vivo* plasma clearance and metabolic effectiveness of α-gal A purified from human spleen and plasma Cohn fraction IV-1. Two patients received six intravenous doses of purified α-gal A over a period of 117 days. Metabolic effectiveness was monitored by measuring circulating Gb_3 levels. Desnick further noted that the described pilot

studies did not demonstrate any side effects or "immunological complications associated with the administration of exogenous enzymes" over a period of nearly four months. Desnick, at 5330. Desnick does not teach the treatment of Fabry's disease by gene therapy or with a small molecule of any kind.

Shiffmann studied the *in vivo* effectiveness of α-gal A purified from the conditioned medium of stably transfected human foreskin fibroblasts expressing human α-gal A using several chromatographic steps. Shiffmann, at 366. Shiffmann monitored metabolic effectiveness of recombinant α-gal A by measuring plasma enzyme concentrations and Gb_3 levels in liver homogenates, plasma and the kidneys. Shiffmann further noted that no "untoward effects" or other complications were observed over the course of the study, and asserted that "[n]one of the patients developed anti-α-gal A antibodies by day 28 post-infusion." Shiffmann, at 367. Shiffmann does not teach the treatment of Fabry's disease by gene therapy or with a small molecule of any kind.

In contrast, Ziegler teaches the treatment of Fabry's disease by gene therapy using an adenoviral vector encoding α-gal A, co-administered with an immunosuppressant. Ziegler noted that identification of the mechanism for secretion and recapture of lysosomal enzymes via the mannose-6-phosphate receptor "provided a therapeutic rationale" for treatment of lysosomal storage disorders "based on **either** enzyme replacement **or** somatic gene therapy." Ziegler, at 1668 (emphasis added). Because recombinant or purified α-gal A has a short half-life and is rapidly cleared from circulation, however, Ziegler noted that treatment requires "frequent readministration with relatively large quantities

of the enzyme[,]" thereby increasing the likelihood of generating an immune response to α-gal A that would prevent further enzyme replacement therapy. *Id.* As a result, Ziegler teaches gene therapy as "[a]n alternative approach that addresses some of the[] limitations" of enzyme replacement therapy.

Like enzyme replacement therapy, gene therapy also requires periodic re-treatment with the gene therapy vector encoding α-gal A. Ziegler teaches that re-treatment overcomes attenuation of α-gal A expression observed approximately 12 weeks post-treatment. *Id.* Ziegler noted that gene therapy with an adenoviral vector has a number of potentially serious side effects, including significant weight loss, hepatic toxicity at high doses, splenic lesions, dose-dependent elevation of serum transaminases and alkaline phosphatase levels, and cellular toxicity resulting from an immune response directed to adenoviral proteins E2a and E4. *Id.* at 1675, 1677-78. To ameliorate these side effects, Ziegler teaches co-administration of recombinant adenovirus expressing α-gal A with one of several immunosuppressive compounds, including cyclophosphamide, FK506 (tacrolimus), deoxyspergualin, soluble CTLA-4Ig, and anti-CD40 antibody. *Id.* at 1679.

In contrast to the combination of Desnick or Shiffmann with Ziegler cited by the Examiner, the claimed invention as amended herein teaches combination therapy to treat lysosomal storage diseases using any two of the following: (1) an exogenously produced natural or recombinant α-gal A; (2) a viral or non-viral vector encoding a α-gal A, and (3) a small molecule that inhibits upstream generation of lysosomal hydrolase substrate. The combination of Desnick or

Shiffmann with Ziegler teaches a method of reducing Gb_3 accumulation with enzyme replacement therapy by the administration of natural or recombinant α-gal A or gene therapy by the administration of a recombinant adenovirus vector encoding α-gal A in combination with an immunosuppressive compound. Because the small molecules of the invention inhibit upstream generation of lysosomal hydrolase substrate to relieve the input burden on the defective enzyme associated with a lysosomal disease and do not suppress the immune system, Applicants respectfully assert that the combination of Desnick or Shiffmann with Ziegler does not teach all the limitations of the claimed invention. Therefore the claimed invention was not obvious to one of ordinary skill in the art at the time of the invention.

Selden teaches treatment of Fabry disease by enzyme replacement therapy or by gene therapy. Purified α-gal A used according to Selden's method is produced by isolated cells transformed with an expression vector encoding full-length α-gal A. In addition, Selden teaches the treatment of patients with such transgenic cells, rather than with a gene therapy vector encoding α-gal A alone. Selden also teaches that, in some cases, treating Fabry disease by gene therapy might require co-administration of an immunosuppressant to prevent a patient's immune response from destroying the transgenic cells. Thus the combination of Desnick or Shiffmann with Selden teaches a method of treating Fabry disease with enzyme replacement therapy by the administration of natural or recombinant α-gal A or with gene therapy by the administration of transgenic cells expressing α-gal A, sometimes in combination with an immunosuppressive compound.

Because the small molecules of the invention inhibit upstream generation of lysosomal hydrolase substrate to relieve the input burden on the defective enzyme associated with a lysosomal disease and do not suppress the immune system, Applicants respectfully assert that the combination of Desnick or Shiffmann with Selden does not teach all the limitations of the claimed invention. Therefore the claimed invention was not obvious to one of ordinary skill in the art at the time of the invention.

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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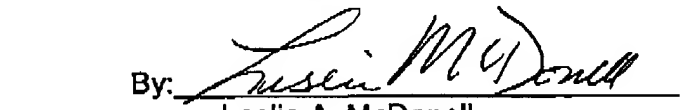
By: 

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